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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,644	12/15/2003	Jay Bua	029488-0112	9030

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/734,644	**Applicant(s)** BUA, JAY	
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 30 May 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-12*.
   Claim(s) withdrawn from consideration: *13-22*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Response to the Amendment

The Amendment filed on 05/30/2006 in response to the previous Non-Final Office Action (02/24/2006) is acknowledged and has been entered.

Claims 1-22 are currently pending.

Claims 13-22 are withdrawn from consideration as being directed to a separately patentable invention from claims already under review.

Claims 1-12 are currently under consideration.

Withdrawal of Claims 13-22 is maintained.

In response to the withdrawal of claims 13-22 as being drawn to subject matter which would require a new search and different consideration for patentability, Applicants assert that the withdrawal of claims 13-22 because they require a new search and different considerations is not a legitimate basis for withdrawing them from consideration. Applicants further assert that the claims were added into the application after a non-final Office action such that the Examiner lacks the authority and the discretion to ignore new claims simply because they present a need for further search and consideration. Significantly, the Examiner did not allege that claims 13-22 are directed to a separately patentably invention from claims already under review. Thus, Applicants urge the Examiner to give claims 13-22 full consideration.

These arguments have been carefully considered, but are not found persuasive.
With respect to Applicants argument's, the Examiner acknowledges that in the previous office action claims 13-22 were withdrawn from consideration because they require a new search and different patentability issues; and further, apologizes for not more clearly setting forth that the claims are directed to a separate and distinct patentable invention. However, the Examiner recognizes that the inventions of claims 1-12 and claims 13-22 represent separate and distinct inventions. For example, claims 1-12 are directed to a method of treatment, classified in class 514, subclass 651, whereas claims 13-22 are directed to a method of diagnosing a breast disease using a mammography, classified in class 378, subclass 37. As such, the inventions of claims 1-12 and 13-22 have acquired a separate status in the art as shown by their different classification. Moreover, the

search required for one group is not required for the other groups because each group requires a different non-patent literature search due to each group comprising different materials and/or method steps. Therefore, claims 13-22 are directed to a separately patentably invention from claims already under review.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 12 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Mauvais-Jarvis (US 4,919,937, 1990, IDS) as evidenced by Mauvais-Jarvis (Cancer Research 1986; 46: 1521-1525) in view of Atkinson et al. (Cancer Epidemiology, Biomarkers & Prevention 1999; 8: 863-866, IDS) as evidenced by Boyd et al. (J. Nat. Cancer Inst. 1995; 87: 670-675) and Kolb et al. (Radiology 2002; 225; 165-175).

In response to this rejection, Applicants contend that the rejection fails to identify any reason for expecting that 4-hydroxy tamoxifen would have the same effect on mammographic breast density as tamoxifen because the two compounds have distinct biological properties and distinct effects. For example, Applicants submit that although 4-hydroxy tamoxifen is a tamoxifen metabolite, its usefulness for reducing breast density is not presaged by previous experience with tamoxifen itself. In contrast, Applicants submit that tamoxifen is extensively metabolized by cytochrome p-450 in humans such that its action in vivo is the net result of individual actions by the parent compound and its metabolite compounds competing for the occupation of receptors within target tissues. Moreover, Applicants assert that each of these compounds manifests different and unpredictable biological activities in different cells, determined in part by each compounds individual

effect on estrogen receptor conformation. For instance, Applicants submit that tamoxifen but not 4-hydroxy tamoxifen is a potent rat liver carcinogen. Additionally, tamoxifen but not 4-hydroxy-tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells. By contrast, Applicants contend that 4-hydroxy tamoxifen exhibits a significant inhibitory effect on estrogen sulphatase activity in mammary cancer cell lines, while tamoxifen has little or no effect in this regard. Applicants acknowledge that 4-hydroxy tamoxifen and tamoxifen are related compounds with similarities. However, Applicants assert that even if those similarities made it obvious to try substituting 4-hydroxy tamoxifen for tamoxifen in reducing breast density (which they did not), "obvious to try" is an incorrect standard for evaluating obviousness. *Hybritech, Inc. v. Monoclonal antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986), cert. Denied, 107 s. Ct. 1606 (1987).* Moreover, the known biological non-equivalence of the two compounds, as discussed above, demonstrates that those skilled in the art would have no reasonable expectation of success using 4-hydroxy tamoxifen in place of tamoxifen.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants contention that the rejection fails to identify any reason for expecting that 4-hydroxy tamoxifen would have the same effect on mammographic breast density as tamoxifen because the two compounds have distinct biological properties and distinct effects, the Examiner acknowledges that each of these two compounds manifest different and unpredictable biological activities in different cells as outlined above (emphasis added). However, the Examiner recognizes that tamoxifen and 4-hydroxy tamoxifen have been individually taught in the prior art to be effective at treating conditions of the breast, including but not limited to, cancer; and further, that percutaneously administered 4-hydroxy tamoxifen is concentrated in the receptor structures of the breast tissue (Mauvais-Jarvis et al. (Cancer Research 1986; 46: 1521-1525). Moreover, the Examiner recognizes that metabolic studies suggest that TAM (tamoxifen) metabolism in vivo involves the conversion to a monohydroxy metabolite form, 4-OHTAM (4-hydroxy tamoxifen), that has a higher affinity for estrogen receptors and is an even more potent estrogen antagonist (antiestrogen) than its precursor tamoxifen (see for example US 4,919,937, column 1, lines 20-32). In addition, the Examiner recognizes that a "population" containing a class III or class IV dense breast composition as recited in the instant claims does not appear to explicitly exclude a patient suffering from breast cancer as evidenced by Atikinson et al. (1999). Thus, one of ordinary skill in the art would have a

reasonable expectation of success that by administering 4-hydroxy tamoxifen percutaneously to a patient having class III or class IV dense breast tissue, e.g., breast cancer, one would achieve method of reducing breast density by treating the breast cancer.

Claim 11 remains rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Mauvais-Jarvis et al. (US 4,919,937, 1990, IDS) as evidenced by Mauvais-Jarvis (Cancer Research 1986; 46: 1521-1525) and Atkinson et al. (Cancer Epidemiology, Biomarkers & Prevention 1999; 8: 863-866, IDS) as evidenced by Boyd et al. (J. Nat. Cancer Inst. 1995; 87: 670-675) Kolb et al. (Radiology 2002; 225; 165-175) in view of Tan et al. (AAPS PharmSciTech 2000; 1; Article 24) and Alberti et al. (Journal of Controlled Release 2001; 71: 319-327).

In response to this rejection, Applicants assert that neither Tan nor Alberti compensates for the deficiencies of Mauvais-Jarvis, Atikinson and the other art, as explained above.

The arguments with respect to Mauvais-Jarvis and Atkinson, as explained above, have been carefully considered, but have not been found persuasive, for the reasons set forth above.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF
July 3, 2006

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER